September 13, 2017

Dr. Tina Bahadori
Director, NCEA
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 8601P
Washington, DC 20460

Re: NTP Mode of Action Research Relevant to the Formaldehyde IRIS Assessment

Dear Dr. Bahadori:

In October 2015, the A merican Chemistry Council Formaldehyde Panel (the Panel) submitted a letter to the previous NCEA Director, Dr. Ken Olden, calling attention to formaldehyde research conducted by the National Toxicology Program (NTP) National Institute of Environmental Health Sciences (NIEHS) which was presented at the 2014 and 2015 Society of Toxicology (SOT) meetings. The NTP research explored a hypothesized mode of action for leukemia in humans using two genetically predisposed strains of mice exposed to formaldehyde and found that formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia. In October 2016, we submitted a follow -up letter to EPA communicating our formal request to NTP to publish the research in a peer-reviewed scientific journal or , at a minimum , for NTP to issue a public technical report. I am pleased to report that in Augus t 2017 , the NTP released a research report titled: Absence of Formaldehyde -Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation,[1] which provides the full details of the research summarily presented at SOT.

The objective of the NTP study was to evaluate the poten tial role of the Trp53 gene in nasal carcinogenicity, leukemia or lymphohematopoietic cancer, and potentially other neoplasms in genetically susceptible mice. Male Trp53 haploinsufficient (Trp53+) mouse strains (B6.129 -Trp53tm1Brd and C3B6.129F1-Trp53tm1Brd) were exposed via inhalation to 0 ppm, 7.5 ppm or 15 ppm formaldehyde for 8 weeks . Because evidence suggests a possible role of the Trp53 gene in formaldehyde -induced nasal squamous cell carcinomas, the authors hypothesized that formaldehyde-induced loss of Trp53 would result in an increase in susceptibility to formaldehyde-induced nasal squamous cell carcinoma, and possibly leukemia and other neoplasms. However, the study found that inhalation of a maximum tolerated dose of formaldehyde did not cause nasal tumors , an increased prevalence of leukemia or lymphohematopoietic cancer , or any other type of cancer in Trp53+ mice. The results from this study increase the weight of evidence that formaldehyde exposure is not causally associated with leukemia. EPA's IRIS Stopping Rules[2] allow for the inclusion of new research information until a few months before an assessment is released for review. This study report provides important information related to postulated modes of action for formaldehyde and should be evaluated and integrated into the formaldehyde weight of evidence framework. We also strongly encourage EPA to reach out to the NTP for additional insight and information on this study.

[1] NTP Research Report on Absence of Formaldehyde-Induced Neoplasia in Trp53 Haploinsufficient Mice Exposed by Inhalation Research Report 3, National Toxicology Program, August 2017. The full report can be found at: https://ntp.niehs.nih.gov/ntp/results/pubs/rr/reports/formaldehyde_508.pdf

[2] EPA IRIS Stopping Rules - https://www.epa.gov/sites/production/files/2014-06/documents/iris_stoppingrules.pdf

EPA has previously indicated that it is committed to ensuring that the revised draft formaldehyde assessment reflects a transparent, rigorous, systematic review of available formaldehyde evidence which is consistent with the 2011 National Academy of Sciences (NAS) recommendations. The Panel has been committed to conducting research to address the recommendations of the NAS and engaging scientists on approaches to integrate the scientific evidence for formaldehyde. As we have previously communicated to EPA, in support of efforts to engage scientific experts on the formaldehyde science and methodologies for integrating the evidence, an invited scientific expert workshop has been scheduled for October 2017. This workshop will provide valuable insight on integrating the formaldehyde science which can inform the EPA's formaldehyde IRIS assessment. We are pleased that EPA IRIS staff accepted an invitation to participate in this workshop and look forward to the discussion.

The methods and approaches that EPA utilizes to systematically review and integrate the science to draw conclusions regarding potential human health risk will be a cornerstone in any future formaldehyde assessment. To help improve our understanding of the processes that will be applied to the formaldehyde assessment, we request that you provide responses to the following questions.

1. How is EPA considering new scientific information, like the NTP study, for incorporation into the weight of evidence for the formaldehyde IRIS assessment?
2. When did EPA last conduct a search of the formaldehyde literature for science to incorporate into the IRIS assessment and how frequently does EPA monitor the formaldehyde literature to identify potential studies that should be incorporated into the assessment?
3. What guidance documents or procedures will EPA utilize to evaluate study quality for studies relied upon to reach conclusions in the formaldehyde IRIS assessment? Please provide specific references if available.
4. When will EPA release a weight of evidence framework illustrating how various data streams (i.e. mechanistic, toxicology and epidemiology studies) are evaluated for quality and then integrated to reach conclusions about formaldehyde?
5. How has EPA addressed all the 2011 NAS recommendations for formaldehyde?
6. How will EPA seek public input and peer review on the formaldehyde IRIS assessment and what types of public meetings or workshops will be held to receive input?

Feel free to contact me by phone (202-249-6707) or email (Kimberly_White@americanchemistry.com) with any questions related to this letter. Additionally, a full copy of the study report is attached for your reference.

Sincerely,

Kimberly Wise White, PhD
American Chemistry Council (ACC)
Senior Director
Chemical Products & Technology Division
On Behalf of the ACC Formaldehyde Panel

Cc:
Robert Kavlock
Dan Morgan
Kris Thayer
Richard Yamada

Attachment 1 – NTP Research Report on Absences of Formaldehyde-Induced Neoplasia in TRP53 Haploinsufficient Mice Exposed by Inhalation, August 2017